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10/517,754	12/13/2004	James B Doherty	20780P	1337

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MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,754	DOHERTY ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☒ Claim(s) *5,9,12 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Lack of Unity

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1.
In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1-18, drawn to pyrimidopyridines of Formula I, in which A is N, D is C, E is NH, classified in class 544, subclass 279, and pharmaceutical compositions thereof and therapeutic methods using compounds of Group I, classified in class 514, subclasses 234.5, 252.14 and 265.1.

II. Claims 1, 2, and 14-18, drawn to Formula I compounds not provided for in Group I (e.g., where A is CH, where E is O, CH2 or CH, where D is N, *inter alia*), classified in various class 544 subclasses, and pharmaceutical compositions thereof and therapeutic methods using compounds of Group II, variously classified in class 514.

Each group as set forth above lacks unity with each other group, i.e., there is no single general inventive concept. The unique special technical features in each group are the identities of the three-nitrogen containing bicyclic ring of Formula I and the other nitrogen containing bicyclic rings of Formula I. The technical relationship among the inventions does not involve at least one common or corresponding special technical feature. The expression "special technical feature" is defined as meaning those

technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art. In this case, a reference that could be used to reject Formula I pyrimidopyridines of Group I could not be used to reject other nitrogen containing bicyclic rings of Formula I of Group II, e.g., benzodiazine (when E is CH2 or CH and D is N) or a benzooxadiazine (when E is O and D is N).

The Group I invention has special technical features not common to Group II and would be expected to be useful other than as disclosed, e.g., as enzyme inhibitors (Bioorganic & Medicinal Chemistry Letters (2003), 13(2), 273-276). Also, the Group II invention has special technical features not common to Group I and would be expected to be useful other than as disclosed, e.g., as quinoline potassium channel inhibitors (U.S. Pat. Pub. 2007/0078154).

A telephone call was made to Mr. Kurt Panzer on March 23, 2007 to request an oral election to the above restriction requirement, and Mr. Panzer elected Group I **with traverse**. Claims 1-18 will be examined only to the extent that they are drawn to the compounds of Formula I, pharmaceutical compositions thereof, and therapeutic methods using compounds of Group I.

To preserve a right to petition, the reply to this Office Action must distinctly and specifically point out supposed errors in the restriction requirement, or the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is

the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 13 is rejected under 35 U.S.C. 112, paragraph 1, Claim 13 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of Formula (I), does not reasonably provide enablement for the compound illustrated in the upper right-hand block (hereinafter referred to as Compound 3). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 13 includes the compound illustrated in the upper right-hand block (hereinafter referred to as Compound 3), which the specification does not teach how to make and use. According to the Formula (I), in Compound 3, E2 is NR. However, the definition of R for the Formula (I) does not permit the cyclopentyl substituent shown for Compound 3. Since the specification enables the compounds of Formula (I) without permitting R to be cyclopentyl, the specification does no enable how to make and use Compound 3.

Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled.

Pursuant to *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue;" see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. The claims cover compounds easily in the billions, as pointed out above.

(b) Scope of the diseases covered. Claim 15 recites a method of treating pain. Claim 16 recites a method of treating rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, or gouty arthritis. Claim 17 recites a method of treating sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome (ARDS), cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, osteoporosis, reperfusion injury, graft v. host rejection, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, AIDS, cachexia secondary to AIDS, ARC (AIDs related complex), keloid formation, scar tissue formation, Crohn's disease (CD), ulcerative colitis, pyresis, or viral infections. Claim 18 recites a method of treating inflamed joints, eczema, psoriasis, inflammatory skin conditions, inflammatory eye conditions or pyresis.

The term "arthritis" is used for any kind of inflammation of the joints arising from a wide diversity of causes and mediators, many of which are unknown. It mostly commonly refers to any of osteoarthritis, gouty arthritis, or rheumatoid arthritis. These are three totally different and unrelated disorders, which all have "arthritis" in their name and involve inflammation of the joints. Rheumatoid arthritis is an inflammatory disorder causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-1, IL-18, α-TNF

and IFN-□. It is thus an autoimmune condition where the body's immune system attacks its joints. In gouty arthritis, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Osteoarthritis is a degenerative cartilage disorder; cartilage breakdown causes bones to rub against each other. Causes include injuries, diseases such as Paget's disease, and long-term obesity, but often the cause is unknown, and the full mechanism has not been discovered. There is also Psoriatic Arthritis (including DIP, and spondylitis) that is believed to be autoimmune in origin but is a separate disorder from RA.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for the recited diseases. As stated above, the compounds enabled by the specification are not representative of the claimed scope but are closer to each other than to the remaining scope. For treatment of arthritis (page 18) or diseases in which cytokines are implicated (page 20), the dosage range is broadly given as 0.01 mg/kg to 100 mg/kg.

(4) State of the Prior Art: The prior art does not recognize compounds of the same activity and similar structure, and no prior art is cited herein against the claims. Because the structure of the present compounds is so unprecedented, the method of

use of the present compounds cannot be extrapolated from what is known of other compounds. In addition, as noted above, the scope of the present compounds comprehends billions of structural permutations.

The state of the art is indicative of the requirement for undue experimentation.

Hashimoto, et al. (J. Pharmacol. and Experim. Therap., Vol. 293, No. 2, pp. 370-375, 2000) studied SB 203580, a pyridinyl imidazole selective inhibitor of p38 MAP kinase activity, in relation to potential therapeutics for ARDS, and concluded the need for further investigations, because the authors could not determine if SB 203580 is capable of producing beneficial effects on ARDS.

Johnson, et al. (Science, Vol. 298, 6 Dec. 2002, 1911-1912) noted p38 pathways as molecular targets for drug development, but only suggested MAPKs as a drug group for potential development in human disease therapy.

In regard to CD, Schreiber, et al., Clin. Gastroenterol. Hepatol., 2006, Mar; 4(3):325-34 (PubMed abstract) concluded, "There was no evidence for clinical efficacy of BIRB 796 [a highly potent inhibitor of p38 MAPK] in CD."

Regarding viral infections, the Viral Defense Found., <http://www.viraldefense.org/mission.htm>, downloaded 5-23-07, states, "Most viral infections are essentially untreatable after infection occurs." Similarly, the Visiting Nurse Assns. of America, <http://www.vnaa.org/vnaa/gen/Germ_Protection_Center_Cold_and_Flu_Resources,html...>, downloaded 5-23-07, notes, "Most viral infections are untreatable..."

Compounds that affect the virus itself, which has not been established here, cannot treat viral infections.

This information indicates the need for undue experimentation to establish enablement for the present claims.

(6) Skill of those in the art: There is no reasonable basis to assume that the myriad of compounds embraced by the broader generic claims all share the same physiological properties, since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 (CCPAS 1966) regarding sufficiency of Markush group disclosure. Also, see MPEP § 2164.03 for enablement requirements in cases directed to structure-sensitive arts, such as the pharmaceutical art.

In terms of the skill on the art of using P38 inhibitors for arthritis, that is very low. Attention is drawn to Boehm, Expert Opinion Therapeutic Patents (2000) 10(1), p 25 of the reference. It is clear from the last paragraph that there is a very low level of knowledge in terms of getting these compounds to actually work. RA is specifically mentioned. However, RA is hardly representative of arthritis generally. Further, such work clearly involves more than routine experimentation. The reference mentions VX-745, which was subsequently dropped from investigations because of adverse effects, and so far as the examiner is aware, the other one, RPR200765A never progressed to clinical trials. As of the filing date, and indeed, so far as the examiner is aware, as of the present date, no one has succeeded in getting a p38 inhibitor to work for any form of arthritis, let alone joint inflammations in general. More broadly, with regard to the

treatment of the various forms of arthritis per se, there is no one single pattern, and some are untreatable. For example, acute attacks of gouty arthritis are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Osteoarthritis appears to result from multiple pathophysiological mechanisms, one of which is the dysregulation of lipid homeostasis. No proven disease-modifying therapy exists for osteoarthritis, in large measure because it cannot be diagnosed until it becomes symptomatic decades after it began, at which point structural alterations are already quite advanced. NSAIDs and COX-2 inhibitors are given for pallation of symptoms, but do not treat the disease per se. Similarly, Hallux rigidus pharmacological treatment is for symptoms only; the disorder itself requires surgery. Neuropathic arthritis is approached by trying to remove the source of the toxin, but cannot always be treated per se. Infectious arthritis is dealt with by treating the underlying infection, when possible.

In addition, the notion that if a disease is mediated by p38, it can necessarily be treated with a p38 inhibitor is medically unsound. This is because cellular processes mediated by kinases often use multiple pathways. For example, p38 has been implicated in regulating neuronal apoptosis but there are other kinases involved as well, especially C-jun N-terminal kinase (JNK), which exists in several isoforms. Indeed, JNK is activated by many of the same apoptotic stimuli that activate p38. For example, expression of protein kinases capable of inducing apoptosis, MEKs and ASK1, can activate both JNKs and p38. Both are activated by Sorbitol and ultraviolet C (UVC) radiation, which in turn induced apoptosis in alveolar type II cells, clear evidence of

multiple pathways. The transcription factors ATF-2 and ATF-a are regulated by both p38 and JNK kinases. Indeed, p38 inhibitor SB202190 also inhibits JNK. The paragraph bridging pages 1-2 of the specification refers to p38 phosphorylation, but there are other kinases which do this as well, e.g. the serine/threonine kinase Akt (or PKB); Akt is also involved in regulating neuronal apoptosis. Similarly, the paragraph notes that p38 regulates TNF, but so do the ERK kinases (both regulate NOS as well).

As evidence of the low skill level in this art, note Dodeller, *Arthritis Research & Therapy* 2006, 8:205 which states: "huge efforts have been made to develop inhibitors of p38 MAPK with the intent to modulate unwanted TNF activity in diseases such as autoimmune diseases or sepsis. However, despite some anti-inflammatory effects in animal models, no p38 MAPK inhibitor has yet demonstrated clinical efficacy in human autoimmune disorders." This demonstrates that a) for p38 MAPK inhibitors, animal models of anti-inflammatory disorders are not a reliable predictor and b) as of 2006, p38 MAPK inhibitors cannot be considered enabled for autoimmune diseases (including rheumatoid arthritis, Rheumatoid Spondylitis and psoriasis).

(7) The quantity of experimentation needed: As insufficient enabling examples are present, there is no clear evaluation of which functional groups at which positions out of the many claimed may affect potency to a greater or lesser degree. For example, the specification only enables compounds of Formula (I) in which A is N, D is C, and E is NH. Compound 3 of claim 13 is not enabled for any utility. See the rejection under 35 USC 112, paragraph 1 *supra*. For compounds of Formula (I) in which A is N, D is C, and E is NH, no compounds are enabled in which R5 is other than hydrogen, in which X

is other than S, in which R3 and R4 are other than halogen, etc. For non-enabled compounds, there obviously has been no testing of their asserted utilities.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 defines "D is C," which would require that the bond between D and E would be a double bond, while E is defined as NH, which would require that the bond between D and E would be a single bond. This is an impossible situation. Correction is required.

Improper Markush Group

Claims 1-18 are rejected as being drawn to an improper Markush Group. The claims are drawn to multiple inventions for reasons set forth in the above holding of

Lack of Unity. This does not constitute an art recognized genus. Because of the marked structural differences at a part of the molecule essential for utility, the claims are deemed to lack unity of invention (see *In re Harnish*, 206 USPQ 300). Claims 1-18 are under examination only to the extent that they are drawn to the compounds of Formula I, pharmaceutical compositions thereof, and therapeutic methods using compounds of Group I. Cancellation of the non-elected subject matter will overcome the rejection.

Objected Claims – Allowable Subject Matter

Claims 5, 9 and 12 are objected to as dependent upon a rejected base claim, but would be allowable if rewritten in independent form to include all limitations of the base claim and any intervening claims.

The subject matter of claims 5, 9, 12 and 13 (other than compound 3, as noted supra) is seen to be patentable over the closest prior art, Natarajan and Fitzgerald, both cited in the International Search Report in corresponding PCT/US2003/017821. Natarajan and Fitzgerald each describe some of the compounds encompassed by present Formula I, however, each of these articles is antedated by the Provisional Application 60/388,066, from which the present application claims priority. It is the Examiner's opinion that the compounds and compositions of Formula I of claims 5, 9, 12 and 13 are not anticipated or obviously suggested by the compounds of Natarajan and/or Fitzgerald.

Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The rejection *supra* under 35 USC 101 explains that claim 13 does not limit the subject matter of claim 1, because claim 1 does not permit R to be cyclopentyl. Applicant is required to cancel Compound 3 from claim 13. Should Applicant wish to amend claims 1 or 13 to claim Compound 3 in proper dependent form, or to claim Compound 3 in independent form, Applicant must substantiate the utility of Compound 3.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-

272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia M. Jaisle, J.D.

Mark L Berch
MARK L BERCH
PRIMARY EXAMINER
GROUP 120 - ART UNIT 1624